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Hypoxia and VEGF up-regulate BMP-2 mRNA and protein expression in microvascular endothelial cells: implications for fracture healing.

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The endothelium is a metabolically active secretory tissue, capable of responding to a wide array of environmental stimuli. Hypoxia and vascular endothelial growth factor (VEGF) are two components of the putative fracture microenvironment. This study investigated the role of hypoxia and VEGF on endothelial cell activation as it relates to the bone repair process. It was hypothesized that endothelial cells may have an important osteogenic role in fracture healing through the production of bone morphogenetic protein-2 (BMP-2), an osteogenic cytokine at the fracture site. Therefore, BMP-2 mRNA and protein expression in endothelial cells under hypoxia and/or VEGF treatment was studied. The authors observed a 2-fold to 3-fold up-regulation of BMP-2 mRNA expression in bovine capillary endothelial cells and human microvascular endothelial cells stimulated with hypoxia or rhVEGF. Furthermore, the combined effects of hypoxia and rhVEGF appeared to be additive on BMP-2 mRNA expression in bovine capillary endothelial cells. Actinomycin D and cycloheximide studies suggested that the increased mRNA expression was transcriptionally regulated. BMP-2 protein expression was up-regulated after 24 and 48 hours of treatment with either hypoxia or rhVEGF in bovine capillary endothelial cells. Surprisingly, the data suggest that endothelial cells may play not only an angiogenic role but also an osteogenic role by a direct stimulation of the osteoblasts, through the enhanced expression of a potent osteogenic factor, BMP-2, at the fracture site.

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